

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 78810032.9

(51) Int. Cl.²: C 07 D 233/58

(22) Date of filing: 19.12.78

C 07 D 233/64, A 61 K 31/415

(30) Priority: 19.12.77 US 861993
05.05.78 US 903155

(43) Date of publication of application:
27.06.79 Bulletin 79/13

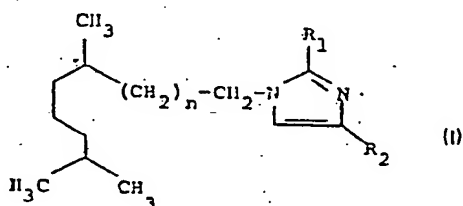
(84) Designated contracting states:
BE CH DE FR GB IT LU NL SE

(71) Applicant: SANDOZ LTD.
Lichtstrasse 35
CH-4002 Basel(CH)

(72) Inventor: Houlihan, William Joseph
15 Raymond Road
Mountain Lakes, N.J.(US)

(54) 1-Dimethyl-substituted alkyl-2- or 4-substituted phenylimidazoles, their production and their use as anti-obesity agents.

(57) This disclosure describes novel compounds of the formula



wherein R_1 and R_2 each represent hydrogen, or, R_3 is hydrogen or fluoro, and n is 1, 2 or 3, and provided that one of R_1 and R_2 is other than hydrogen which are useful as anti-obesity agents.

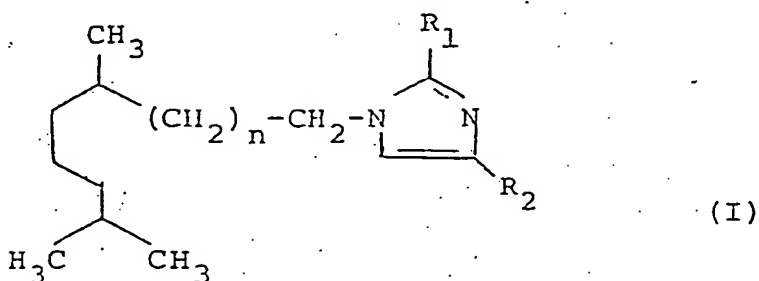
EP 0 002 649 A2


1-DIMETHYL SUBSTITUTED ALKYL-2- OR 4-SUBSTITUTED
PHENYLIMIDAZOLES, THEIR PRODUCTION AND THEIR USE
AS ANTI-OBESITY AGENTS

This application relates to 1-dimethyl-substituted alkyl-2- or 4-substituted phenylimidazoles which are useful as anti-obesity agents. In particular, it relates to 1-dimethyl-substituted alkyl-2- or 4-substituted-phenylimidazoles and their pharmaceutically acceptable acid addition salts.

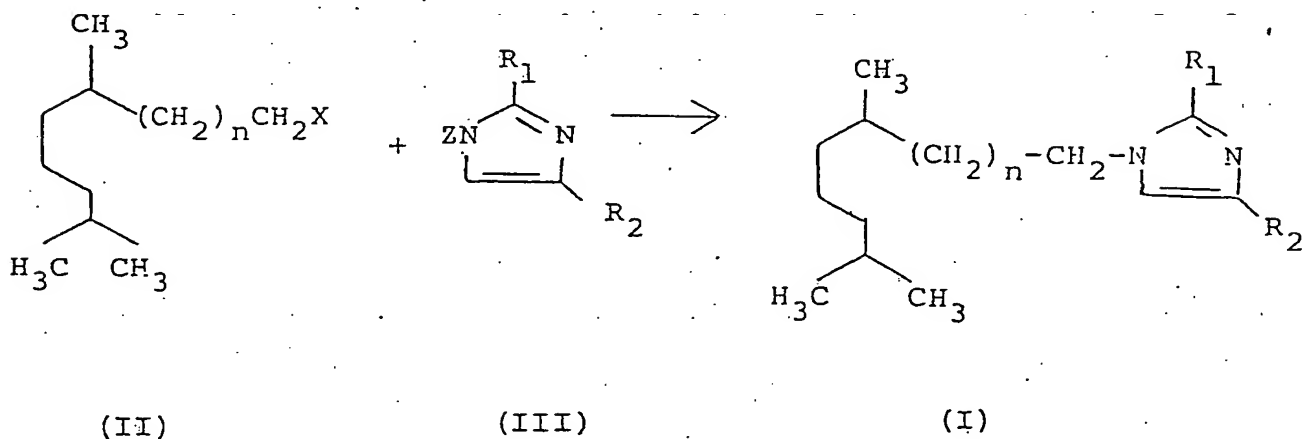
5

The compounds of this invention may be represented by the following structural formula:

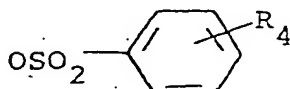


wherein R_1 and R_2 each represent hydrogen, or R_3 , and R_3 is hydrogen or fluoro, and n is 1, 2 or 3, and provided that one of R_1 and R_2 is other than hydrogen.

The compounds of formula (I) may be prepared according to the following reaction scheme:



where X is halo having an atomic weight of about 35 to 127 or



wherein R_4 is hydrogen, chlorine, or methyl,
 Z is sodium, potassium or lithium, and
 R_1 , R_2 , n and the proviso are as defined above.

The compounds of formula (I) are prepared by
5 treating a compound of the formula (II) with a compound of the
formula (III) under an inert atmosphere preferably nitrogen
in the presence of an inert organic solvent. Although the
particular solvent employed is not critical, the preferred
solvents include the aromatic hydrocarbons such as benzene,
10 toluene and the like, the ethers such as dioxane, tetrahydro-
furan and the like, dimethylacetamide and dimethylformamide,
the latter being especially preferred. The temperature of
the reaction is not critical, but it is preferred that the
reaction be carried out between about 15° to 60°C., preferably
15 from about 20° to 30°C. The reaction may be run from about 8
to 36 hours, preferably from about 12 to 20 hours. The pro-
duct is recovered using conventional techniques, e.g., dis-
tillation or crystallization or when necessary, column chro-
matography followed by distillation or crystallization.

20 The compounds of formulae (II) and (III) are known
and may be prepared by methods described in the literature.

It will be understood that the compounds of formula
(I) may exist in the form of optically active isomers which
can be separated and recovered by conventional techniques,
25 and such isomeric forms are also included within the scope
of this invention.

The compounds of formula (I) are useful because
they possess pharmacological activity in animals. In par-
ticular, the compounds of formula (I) are useful as anti-

obesity agents in the treatment of obesity as indicated by preventing an increase in the blood sugar level in male Wistar rats in groups of 4 which are fasted for 16 hours and then are given an initial dose of 200 milligrams per kilogram of animal body weight of the test compound orally. One hour later, the rats are given 2.5 grams per kilogram of animal body weight of starch load. Thirty minutes after administration of the starch, the rats are anesthetized with 120 milligrams per kilogram of animal body weight of sodium hexobarbital after which blood is collected via cardiac puncture. The blood samples are placed in an autoanalyzer cup containing 0.1 milliliters of heparin (1,000 units per milliliter). The heparinized blood is used to determine the blood sugar level with an autoanalyzer. The blood sugar content is compared to the control group which receives 0.5% carboxymethyl cellulose and are run concurrently. The blood sugar levels are calculated and compared to the control.

For such usage, the compounds of formula (I) may be combined with a pharmaceutically acceptable carrier or adjuvant and may be administered orally or parenterally as such or admixed with conventional pharmaceutical carriers. They may be administered in such forms as tablets, dispersible powders, granules, capsules, syrups and elixirs, and parenterally as solutions, suspensions and the like, e.g., a sterile injectable aqueous solution. The dosage will vary depending upon the mode of administration utilized and the particular compound employed.

The compounds of formula (I) may be similarly administered in the form of their non-toxic pharmaceutically accept-

able salts. Such salts possess the same order of activity as the free base and are readily prepared by reacting the base with an appropriate acid and accordingly, are included within the scope of this invention. Representative of such salts are the mineral acid salts such as the hydrochloride, hydrobromide, sulfate, phosphate and the like and the organic salts such as the succinate, benzoate, acetate, p-toluenesulfonate and the like.

The anti-obesity effective dosage of active ingredient employed for the treatment of obesity may vary depending on the particular compound employed, the mode of administration and the severity of the condition being treated. However, in general, satisfactory results are obtained when the compounds of formula (I) are administered at a daily dosage of from about 2 milligrams to about 400 milligrams per kilogram of animal body weight, p.o., preferably given in divided doses two to four times a day, or in sustained release form. For most large mammals, the total daily dosage is from about 25 to about 1000 milligrams. Dosage forms suitable for internal use comprise from about 7.5 to about 500 milligrams of the active compound in intimate admixture with a solid or liquid pharmaceutically acceptable carrier or diluent.

A representative formulation suitable for oral administration two to four times a day for the treatment of obesity is a capsule prepared by standard encapsulating techniques which contains the following:

INGREDIENTS	WEIGHT (mg.)
(±)-1-(3,7-dimethyloctyl)-2-phenylimidazole	100
inert solid diluent (starch, lactose, kaolin)	200

EXAMPLE 1.

(±)-1-(3,7-dimethyloctyl)-2-phenylimidazole.

To a solution of 21.5 g. (0.14 mole) of 2-phenyl-
imidazole in 60 ml. dry dimethylformamide and 300 ml. dry
tetrahydrofuran under nitrogen atmosphere there is added at
room temperature 9.0 g. (0.19 mole) of 50% sodium hydride/
mineral oil suspension. The resulting mixture is stirred
and heated to 50°C. for about 3 hours. After cooling to
room temperature the resulting mixture is treated dropwise
with a solution of 40.5 g. (0.18 mole) of (±)-1-bromo-3,7-
dimethyloctane in dry tetrahydrofuran. The reaction mixture
is stirred over night at room temperature and the resulting
mixture is filtered and the residue washed with tetrahydro-
furan. The combined filtrate is concentrated in vacuo to
an oil, the oil is then dissolved in methylene chloride,
washed with water, dried over anhydrous sodium sulfate,
filtered and concentrated in vacuo to yield an oily product.
Distillation gave (±)-1-(3,7-dimethyloctyl)-2-phenylimidazole;
b.p. 150° to 157°C. at 0.2 - 0.16 mm.

Following the above procedure and using in place of
2-phenylimidazole an equivalent amount of

- a) 2-(p-fluorophenyl)imidazole, or
- b) 4-phenylimidazole

there is obtained

a) (\pm) -1-(3,7-dimethyloctyl)-2-(p-fluorophenyl)
imidazole or

b) (\pm) -1-(3,7-dimethyloctyl)-4-phenyl
imidazole b.p. 155° to 165°C at 0.2 mm respectively.

Also following the above procedure and using in
place of (\pm) -1-bromo-3,7-dimethyloctane an equivalent
amount of

c) (\pm) -1-bromo-4,8-dimethylnonane, or

d) (\pm) -1-bromo-5,9-dimethyldecane,

there is obtained

c) (\pm) -1-bromo-4,8-dimethylnonane, or

d) (\pm) -1-bromo-5,9-dimethyldecane,

there is obtained

c) (\pm) -1-(4,8-dimethylnonyl)-2-phenylimidazole, or

d) (\pm) -1-(5,9-dimethyldecyl)-2-phenylimidazole,

b.p. 142-148° at 0.7 mm.

Also following the above procedure and using in
place 2-phenylimidazole an equivalent amount of 4-phenyl-
imidazole and using in place of (\pm) -1-bromo-3,7-dimethyl-
octane an equivalent amount of (\pm) -1-bromo-5,9-dimethyl-
decane there is obtained

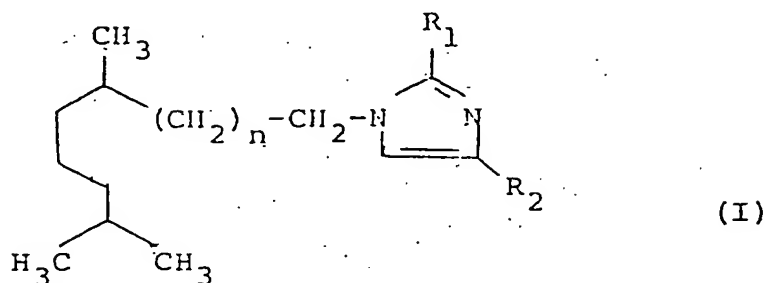
c) (\pm) -1-(5,9-dimethyldecyl)-4-phenylimidazole


b.p. 195° to 205°C at 0.5 mm.

The (\pm) -1-(3,7-dimethyloctyl)-2-phenylimidazole of
this example is an effective anti-obesity agent when orally
administered to an animal in need of said treatment at a
dosage of 150 mg. two to four times a day.

WHAT IS CLAIMED IS:

1. A compound of the formula



wherein R_1 and R_2 each represent hydrogen, or R_3 , and R_3 is hydrogen or fluoro, and n is 1, 2 or 3, and

provided that one of R_1 and R_2 is other than hydrogen or a pharmaceutically acceptable acid addition salt thereof.

2. A compound of claim 1 in free base form.

3. A compound of claim 1 in which R represents hydrogen.

4. The compound of claim 1 which is (+)-1-(3,7-dimethyloctyl)-2-phenylimidazole.

5. The compound of claim 1 which is (+)-1-(5,9-dimethyldecyl)-2-phenylimidazole.

6. The compound of Claim 1, which is
(±)-1-(3,7-dimethyloctyl)-4-phenylimidazole.

7. The compound of Claim 1, which is
(±)-1-(5,9-dimethyldecyl)-4-phenylimidazole.

5

8. A pharmaceutical composition for use in the
treatment of obesity, which comprises an anti-obesity
effective amount of a compound of Claim 1 and a pharma-
ceutically acceptable diluent or carrier therefor.

3700/MO/HD

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☒ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☒ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.